Remarks/Arguments

Claims 33-34, 36-37, 43-50, 59-65, 71-78, and 87-120 are pending in the application and stand rejected. Claims 121-128 are new. Independent Claims 121 and 123 include no explicit recitation that the level of the enzyme is maintained in the first cell line and the test cell respectively. Maintenance of the level of the enzyme is implicit in the method to identify inhibitors or activators because the phenotypic response (i.e. the responsively changing phenotypic characteristic) that the skilled investigator first defines and selects in the Test cell prior to practicing the method will not be present unless the level of the enzyme is maintained in the Test cell. The specification teaches that the essential phenotypic response can be provided by stable overproduction of the enzyme. As an alternative to specifying that the level of the enzyme be maintained, new independent Claims 125 and 127 recite that the enzyme is not down-regulated in the presence of a specific inhibitor or activator of the enzyme. Support is found, for example, at page 35, line 30 to page 36, line 5 of the Specification.

Attached hereto is a Declaration under 37 C.F.R. § 1.132 of Dr. James D. Griffin ("the Griffin Declaration").

Rejection Under 35 U.S.C. § 112, first paragraph – (new matter)

Claims 33-34, 36-37, 43-50, 59-65, 71-78 and 87-120 stand rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement. The Examiner has asserted that there is no support in the specification for limitations concerning the level of the target enzyme in the cell when in contact with a potential inhibitor or activator, and further that the exclusion of certain inhibitions constitutes new matter. The rejection is respectfully traversed.

The Applicant has pointed out the significance of the concept of the responsive phenotypic change on numerous occasions and directed the Examiner's attention to portions of the specification that state or otherwise support that significance. The phenotypic change arises from the activity of the POI as it functions in a cell. The POI is expressed at a level sufficient to evoke an observable (measurable) phenotypic change that is responsive to the amount of the POI and to the activity of the POI. The sensitivity of the phenotypic change to

activators and inhibitors of the POI is dependent on the amount of the POI in the cell. The specification explains that the response should be proportional to the level of production of the POI. The specification also states that the host cells should exhibit a readily observable phenotypic change as a result of enhanced production of the POI.

The importance of stable overproduction of the POI is also discussed. For example, the specification provides that cells that stably overproduce a POI will exhibit a graded cellular response. Specification, page 4, lines 13-16, page 4, line 35 to page 5, line 2. The working examples also point out the importance of stable overexpression. For example, test cells that overexpress PKC show exaggerated morphological changes in response to TPA and that characteristic persists over the course of the experiment. Significantly, the cells do not display the usual refractory response to TPA which is due to down-regulation of the POI in cells in which production of the POI is not controlled. Thus, in the Test cells in which the overproduction of the POI is at a higher, usually non-naturally occurring level and is relatively stable, the phenotypic response will continue to be modulated despite multiple applications of a given activator or inhibitor.

The Applicant has attempted to incorporate stable overproduction and absence of down-regulation (*i.e.* persistence of the responsive phenotypic change for the duration of the experiment) into the claims. In this respect, the claims were amended to recite that "the level of the enzyme is maintained such that the cell is capable of exhibiting the phenotypic response following removal of a direct activator or inhibitor of the enzyme." The Examiner's response was that such language was vague because it was unclear if the enzyme [POI] had to be maintained in an active form in the cell when in the presence of (and bound to) the inhibitor.

In an effort to specify that the enzyme persisted in a potentially active though inhibited state when the inhibitor was present, the claims were amended to recite that the level of the enzyme activity in the cell is maintained. Even though the amendment explained what was intended, the Examiner stated that the limitation appeared to require that the target enzyme be enzymatically active in the cell in the presence of the inhibitor or activator, but that it was unclear whether there would be any phenotypic change if the enzyme is enzymatically active when bound to the inhibitor.

In an effort to specify that the level of the enzyme remains essentially unchanged, but taking into account the Examiner's assertions regarding enzyme activity, the claims were then amended to specify that "the level of the enzyme in the cell is maintained such that the cell remains capable of exhibiting the phenotypic response following removal of a direct activator or inhibitor of the enzyme." The Examiner has now stated that the claims appear to require that the level of the enzyme be maintained before the inhibitor is added, during the period the inhibitor is present, and after the inhibitor is removed. However, the Examiner has misinterpreted the Applicants statements regarding enzymatic activity. The Applicant was simply stating that an enzyme is not active and inhibited at the same time, as the Examiner's argument would suggest.

Nevertheless, it appears that the Examiner now correctly states what is meant to be claimed when he observes that "the claims appear to require that the level of the enzyme be maintained before the inhibitor is added, during the period the inhibitor is present, and after the inhibitor is removed." However, contrary to the Examiner's assertion concerning new matter, there is support for limitations concerning the level of the target enzyme in the cell when in contact with an inhibitor or activator. In particular, the Examples provide test cells in which the level of PKC is maintained when in contact with an inhibitor or activator.

Rejection Under 35 U.S.C. § 102

Claims 33-34, 36, 43-44, 46-47, 49, 63-64, 71-72, 74-75, 77, 88, 90-92, 94-95, 97-98, 100, 106-107, 109-110, 112-113, 115, and 118 are rejected as anticipated by Drebin. The Examiner states that Drebin notes that the level of the enzyme is maintained such that the cell is capable of expressing p185 and exhibiting the phenotypic response after removal of the inhibitor, i.e., that the level of the enzyme is maintained such that the cell remains capable of exhibiting the phenotypic response following removal of the inhibitor. The rejection is respectfully traversed.

As the Examiner has pointed out, the claims appear to the claims appear to require that the level of the enzyme be maintained before the inhibitor is added, during the period the inhibitor is present, and after the inhibitor is removed." In Drebin, the level of the enzyme is not maintained during the period the inhibitor is present. As discussed above, and as should be apparent from Applicant's complete remarks in the prior amendment, the enzyme activity

(*i.e.*, uninhibited in the absence of inhibitor, inhibited in the presence of inhibitor) is maintained in the cell such that the test cell continues to display the responsive phenotypic change even after the inhibitor is removed, unlike Drebin.

In Drebin, p185 enzyme is reduced during the time that the cell is treated with an anti-p185 antibody (the "inhibitor") is present. Further, the cell does not continue to display the phenotypic response following removal of the inhibitor, but only after an extensive period of time (approximately a day) sufficient for the cell to recover from the treatment, re-synthesize the p185 cell-surface receptor, and thereby restore the level of p185 enzyme activity. There are no such requirements with Applicant's invention. Accordingly, Drebin does not anticipate the claimed invention and the rejection should be withdrawn.

Rejection Under 35 U.S.C. § 112, first paragraph - enablement

Claims 33-34, 36-37, 43-50, 59-65, 71-78 and 87-120 stand rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement. Specifically, the Examiner alleges that specification does not provide enablement for a method of identifing a direct inhibitor or activator of a particular protein because a skilled artisan would not be able to distinguish chemical agents which act indirectly to inhibit or activate the target protein or enzyme of interest (POI) from agents which directly interact with the POI so as to inhibit or activate the POI without undue experimentation. Applicant respectfully traverses the rejection.

It is implicit to the invention that as a result of the overproduction of the enzyme in the Test cell the resulting ***phenotypic response*** (i.e. the ***responsively changing phenotypic characteristic***) that the skilled investigator first defines and selects in the Test cell prior to practicing the method will inherently distinguish between activators or inhibitors that interact with (bind to) the target enzyme versus chemical agents that interact with other proteins or non-protein targets within the cell. The specification teaches that stable overproduction is a way to evoke the *phenotypic response* that is indeed capable of distinguishing between chemical inhibitors or chemical activators of the target enzyme as opposed to chemical agents which affect other proteins or non-protein targets in the cell.

The Examiner has referred to Hsiao et al. and Ledwith et al. as illustrative of the unpredictable nature of using phenotypic changes associated with expression of a target POI

for identifying direct inhibitors or activators of a POI and that such methods can actually result in identification of agents which do not interact with the target, but instead interact with another target.

The instant specification already acknowledges that, absent Applicant's invention, methods in the art that employed phenotypes to identify active substances were not specific with respect to any cellular component. Griffin Declaration, ¶4. The Applicant's invention provides the specificity otherwise lacking in the art. Griffin Declaration, ¶5.

The Applicant's identification and use of a graded cellular response enables one of ordinary skill in the art to identify substances which are modulators of the POI that evokes the graded cellular response. This specific type of change in a phenotypic characteristic allows the identification of modulators that act directly on the POI instead of modulators that act on other cellular components. Griffin Declaration, ¶12.

Hsiao neither identifies nor makes use of a graded cellular response or any other responsive change in a phenotypic characteristic. Hsiao's method does not rely on any association between POI level and phenotype that would enable one of ordinary skill to predictably identify compounds that directly activate or inhibit $p21^{ras}$. Griffin Declaration, ¶15. Ledwith also has neither identified nor has used a "graded cellular response" or any other responsive change in a phenotypic characteristic. Ledwith has only established a relationship between a protein in a cell that is not the POI (not the level of that protein) and the level of a compound that reduces the amount of that protein. Griffin Declaration, ¶¶17, 18.

The cited articles, and the art in general, do not support the Examiner's contention because the art does not teach how to evoke or use the specialized phenotype provided by the Applicant's invention. One of ordinary skill in the art, having read Housey's specification, would not be misled by Hsiao's or Ledwith's articles into believing that any substance tested according to Hsiao's method was a direct activator or inhibitor of a POI. Griffin Declaration, ¶¶16, 19.

The Applicant has provided working examples to demonstrate that chemical agents that directly modulate a POI cause changes in a specialized phenotype that is observable when the POI is overexpressed. In particular, the specification demonstrates that where the

POI is the β isoform of protein kinase C, direct inhibitors of protein kinase C reduce the phenotypic change in the cells in a graded manner. Using the same specialized phenotype, the specification also demonstrates that tamoxifen is a direct inhibitor of protein kinase C. Griffin Declaration, ¶11.

The Examiner has suggested that whether tamoxifen actually was a direct inhibitor of PKC had to be determined using an *in vitro* binding assay. To the contrary, the experiments disclosed in Applicant's specification established that tamoxifen is a direct inhibitor of PKC. The originally filed specification referred to O'Brian et al., Cancer Res., 1985, Vol. 45. No. 6, pp. 2462-2465, which provided only that tamoxifen inhibited PKC activity in a cell free assay that was not free of other cellular components. It was only in response to the Examiner's disbelief that the invention worked as claimed that the Applicant subsequently brought to the Examiner's attention O'Brian et al., Cancer Res. 1988, Vol. 48, No. 13, pp. 3626-3629 which showed specific and direct binding of PKC to a tamoxifen analog.

The Examiner has also referred to the Decision of the Technical Board of Appeal of the European Patent Office in case T 0729/00 3.3.4. Of note, the decision of the Opposition Division of the European Patent Office which was the basis for the appeal was unanimously in favor of the Patentee. Also, the claims before the Technical Board of Appeal were not the instant claims. Lastly, the decision of the Technical Board of Appeal is not binding on the Patent Office.

In summary, the Applicant's invention, as disclosed and claimed, allows one of ordinary skill in the art to identify activators and inhibitors of a POI. It is respectfully requested that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 112, first paragraph – written description

Claims 33-34, 36-37, 43-50, 59-65, 71-78, and 87-120 stand rejected under 35 USC § 112, 1st paragraph, as failing to comply with the written description requirement. The Examiner continues to assert that the claims contain subject matter that is not described in the specification in a way that conveys possession of the claimed invention to one of ordinary skill in the art.

As set forth above, the Specification discloses a method that discriminates chemical agents that directly interact with a POI. The specification teaches the elements that are critical to that discrimination and provides working examples that incorporate those elements. Most importantly, as pointed out above with regard to enablement, the specification sets forth the features that were lacking in the art, which make the disclosed cell based assays for identification of direct (specific) inhibitors or activators of an enzyme a reality.

In view of the arguments in this amendment and already of record, the Applicant asserts that the claimed invention complies with the written description and respectfully requests reconsideration and withdrawal of the instant rejection

Conclusion

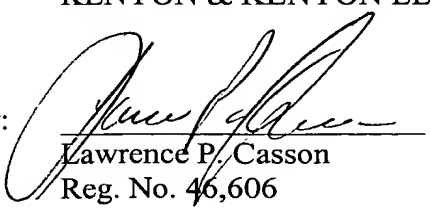
It is believed that this amendment is fully responsive to the Examiner's rejections. Applicant feels that all references cited by the Examiner have been distinguished from the claimed subject matter. Should the Examiner find another reference which allegedly describes the invention and suggests that enablement is lacking, it is requested that the Examiner please contact the undersigned to arrange an interview so as to expedite prosecution.

In view of the foregoing amendments and remarks, it is firmly believed that the subject claims are in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

KENYON & KENYON LLP

Date: April 5, 2006

By: 
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